

### **REMARKS**

Prior to the present amendment, claims 26-28 and 33-35 were pending. Claims 1-20, and 29-32 were previously canceled. By the present amendment, claims 26, 34, and 35 were amended. No new matter has been added. Accordingly, claims 26-28, 33-35 remain under consideration.

#### **Rejection under 35 U.S.C. § 103**

On pages 2-10 of the office action, the examiner rejects various combinations of claims 26-28 and 33-35 as being unpatentable under 35 U.S.C. § 103(a) over Eschenfelder (*US 4,944,943*) and Baldwin (*US 5,098,707*) and additional cited references. Applicants respectfully disagree.

Eschenfelder teaches that his “present invention relates to a mixture of a substance having thrombolytic activity and of an antithrombotic substance” (col. 1, lines 23-25). In addition, the only reference to treatment of “hemorrhoidal thrombosis” in Eschenfelder concerns “the mixture” (col. 2, lines 38-41):

The mixture is therefore suitable for the treatment of thromboses of any type, such as thrombophlebitis, hemorrhoidal thrombosis, pulmonary embolism and infarct.

Baldwin and the remaining cited references fail to compensate for the deficiencies of Eschenfelder. For example, the only disclosure regarding rectal administration is in Baldwin, which concerns administering “suppository compositions [that] comprise an imidazole compound in a pharmaceutically acceptable carrier” (col. 23, lines 65-68, Baldwin). As acknowledged by the examiner on page 4 of the office action, Baldwin is devoid of any disclosure or suggestion of a method for treating hemorrhoid disease.

In the passage cited by the examiner (i.e., col. 24, lines 1-35), Baldwin discloses preparation of suppositories with conventional carriers. However, in the paragraph immediately preceding the passage that was cited by the examiner, Baldwin describes such compositions as a mixture. See col. 23, lines 65-68 of Baldwin:

Compositions to be employed in the practice of the present invention whether parenteral, oral or suppository compositions comprises an imidazole compound in a pharmaceutically acceptable carrier.

(emphasis added).

The examiner also cites the abstract of Baldwin, which also teaches a mixture:

Compositions useful for thrombolytic therapy comprising a plasminogen activator such as tPA or streptokinase together with an imidazolium salt...

Accordingly, the methods described in Eschenfelder and Baldwin, and the remaining art references, individually and in combination, require an additional active compound for use in treatment. The references do not read upon the claimed compositions "consisting essentially of" a thrombolytic protein. "All words in a claim must be considered in judging the patentability of that claim against the prior art." *MPEP* § 2143.03.

"The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." *MPEP* § 2143.01. In the present case, the mere fact that thrombolytic proteins can be omitted from Eschenfelder and Baldwin and/or the remaining art references does not obviate the claimed invention because none of the cited references provided any evidence of predictability in an effective method for treatment of hemorrhoid disease in a human through rectal administration. Every one of the methods of treatment disclosed in Eschenfelder and Baldwin relates to a composition that includes an additional active compound.

In fact, the modification of the Eschenfelder and Baldwin references as proposed by the examiner would not have yielded any predictable results concerning treatment of hemorrhoid disease through rectally administered compositions consisting essentially of thrombolytic proteins. The Yamamoto reference submitted with the IDS of January 21, 2009, states the possibility of:

...incomplete absorption [of peptides and protein drugs]...due to a combination of poor membrane permeability and metabolism at the absorption site. Thus, a number of absorption enhancers have been utilized for improving rectal absorption of larger polypeptides and proteins.

(p. 276 of Yamamoto). The Yamamoto reference also indicates the presence of proteases at the area of rectal absorption such as trypsin (p. 282, Figure 3, and p. 276 first full paragraph on the left-hand column of Yamamoto).

Moreover, the Castellanos-Serra reference (*Electrophoresis*, 2002 Jun;23(11):1745-53), submitted in an IDS on July 7, 2009, states on page 1751 that streptokinase is “a 47 kDa protein that has proven to be highly sensitive to proteolytic degradation, even under native conditions. There are several reasons for this high susceptibility towards proteolysis: this 414 amino acids protein has 52 tryptic...cleavage sites...”

Thus, there was an expectation of incomplete absorption and/or proteolysis of the thrombolytic proteins by the proteases at the site of rectal administration. The thrombolytic proteins were known to be highly susceptible to proteolytic degradation, and rectal administration of protein drugs has been hampered by the presence of proteases. There was no predictability regarding rectal administration of a composition consisting essentially of a thrombolytic protein.

Contrary to the examiner's allegations, mere existence of a composition consisting essentially of a thrombolytic protein at the time of the invention is not evidence that it was predictable in the art to administer rectally such a composition in a method to treat hemorrhoid disease effectively. The claims require that the treatment is effective.

"The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." *MPEP § 2143.01*. Based on the cited art references, nothing was predictable regarding an effective treatment of hemorrhoid disease by rectally administering a thrombolytic protein, without an additional active compound.

Nothing in the cited art references evidences that an omission of the additional active compound in the respective "mixtures" would predictably treat hemorrhoid disease and be effective to reduce pain, swelling, and itching due to hemorrhoid disease. As stated above, none of the unpredictable factors concerning rectal administration of a protein were addressed in either reference. See *MPEP § 2143.01* ("If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification").

Merely to expedite prosecution, applicants have amended the claims to include a requirement that the treatment is "effective to reduce pain, swelling, and itching due to hemorrhoid disease." Support for the claim amendment can be found throughout the specification. See, for example, Example 5 on pages 11-13 and Table 2 on page 12 of the originally filed specification.

As explained in § 2143.02 of the MPEP, a *prima facie* case of obviousness requires a showing of a reasonable expectation of success. The Office Action has not established a *prima facie* case of obviousness. No reasons were set forth to explain why one of skill, given the combination of cited references and common knowledge in the art, would have had a reasonable expectation of success in practicing the claimed methods.

For example, the Office Action does not point out why one skilled in the art would reasonably expect that a rectally administered protein would be effective to reduce pain, swelling, and itching due to hemorrhoid disease, when there was an expectation of incomplete absorption and/or proteolysis of the rectally administered protein at the time of the invention (Yamamoto). Without more, one of skill would have had no reason to select a composition consisting essentially of a thrombolytic protein in order to treat hemorrhoid disease via rectal administration.

As explained in the Examples of the present application, Applicants discovered that rectally administering a composition consisting essentially of a thrombolytic protein surprisingly leads to an effective treatment of hemorrhoid disease. Specifically, they discovered that the composition is, *inter alia*, effective to reduce pain, swelling, and itching due to hemorrhoid disease. Therefore, the claimed methods represent an unexpected result. The office action has not cited a sound basis in the art for these surprisingly effective and unexpected activities.

Accordingly, the combination of cited references fails to obviate every element of the claims. In addition, the mere fact that the references can be modified does not render the claimed invention obvious when rectal administration of a thrombolytic protein would have been unpredictable and possibly detrimental to the activity of the protein. Moreover, there is no suggestion or motivation to make the proposed modification of omitting additional active components since the proposed modification would render at least the Eschenfelder and Baldwin inventions unsatisfactory for their intended purposes. Therefore, the cited references, individually and in combination, fail to obviate the claimed invention under 35 U.S.C. § 103. Applicants respectfully request reconsideration and withdrawal of the rejection.

### **Conclusion**

In view of the foregoing amendments and remarks, entry of the amendments and favorable consideration of the claims are respectfully requested. If the examiner has any questions or concerns regarding this amendment, she is invited to contact the undersigned at the telephone number listed below. If any fees are due or any overpayment made in connection with this paper, please charge or credit our Deposit Account No.: 082461.

Respectfully submitted,

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